SAVE BLOOD, SAVE LIVES

Transfusions are one of the most overused treatments in modern medicine, at a cost of billions of dollars. Researchers are working out how to cut back.

BY EMILY ANTHES

In 2009, a major California hospital was looking for ways to cut costs. Stanford Hospital and Clinics was on track that year to purchase nearly US$6.8 million worth of blood for transfusions. But a growing body of evidence was suggesting that physicians could often forego the procedure.

So, beginning in July 2010, whenever a clinician used the hospital's computerized ordering system to request blood, it would call up the patient's most recent lab results. If the numbers indicated that she or he should be healthy enough to get by without a transfusion, an alert would pop onto the screen gently reminding the doctor of the guidelines and requesting further justification for the order.

The results, detailed in two papers published in the past 18 months[1,2], were dramatic. The number of red-blood-cell transfusions dropped by 24% between 2009 and 2013, representing an annual savings of $1.6 million in purchasing costs alone. And as transfusion rates fell, so did mortality, average length of stay and the number patients who needed to be readmitted within 30 days of a transfusion. By simply asking doctors to think twice about transfusions, the hospital had not only reduced costs, but also improved patient outcomes.

Transfusions are common procedures, at least in developed nations. In 2011, US doctors transfused 21 million units of blood and blood products; in the United Kingdom, the number was nearly 3 million. But although transfusions can be lifesaving, they are often unnecessary and are sometimes even harmful. "I think we were kind of brainwashed into thinking that blood saves lives, and the more you give the better," says Steven Frank, an anaesthesiologist and director of the blood-management programme at the Johns Hopkins Health System in Baltimore, Maryland. "We've gone 180 degrees, and

PHOTOGRAPH BY GREG WHITE

now we think that less is more."

Scientists are now recommending a more conservative approach to transfusions. But changing decades of established medical practice is not easy. Even when guidelines are clear, evidence suggests that clinicians often fail to follow them. "Weaning doctors off their love affair with blood is going to be harder than we think," says Ian Roberts, director of the Clinical Trials Unit at the London School of Hygiene & Tropical Medicine.

TRANSFUSION TRIGGERS

Significant blood loss — as well as conditions ranging from leukaemia to vitamin deficiencies — can leave body tissues starved of oxygen. Transfusions of red blood cells collected from compatible donors are designed to reverse this state. (Some patients may receive transfusions of other blood components, such as platelets, which help with clotting, but red-cell transfusions are by far the most common.)

Scientists and doctors have experimented with transfusion since at least the seventeenth century, but the procedure did not become routine until the early 1900s, after researchers found that there were different blood groups and learned how to store donated blood. Blood banking really took off during the Second World War. In Britain, collection teams travelled around the country, tapping citizens' arms to help soldiers on the front lines. "Will you help by giving a little of your blood?" a 1944 poster implored. "The lives of our wounded depend upon it." By the end of the war, more than 750,000 people had heeded the call, some donating seven or eight times.

In the decades since, appeals for blood have become common, particularly in times of war or disaster. But transfusions were widely adopted without rigorous scientific scrutiny. At the time, randomized controlled trials were not standard, and the rationale for transfusion seemed obvious. "I think people took blood for granted," Roberts says. "They thought 'Well, if people are losing blood then they must need blood'."

In the 1980s and 1990s, a confluence of factors sparked interest in cutting back. The discovery of the blood-borne hepatitis C and HIV raised concerns about the safety of transfusions. The resulting expansion of testing for infectious diseases increased the cost of collection, and toughened screening standards contributed to a decline in donations. Some clinicians began to wonder if they could get by with less.

In 1994, a team of Canadian researchers launched a study to evaluate how patients would respond to more sparing use of blood. Doctors typically decide whether to do a transfusion by measuring a patient's level of haemoglobin, the protein inside red blood cells that binds to oxygen. The World Health Organization defines a healthy haemoglobin level as 13 grams per decilitre ($g\,dL^{-1}$) of blood or higher in men, and $12\,g\,dL^{-1}$ in women. Historically, doctors would consider a transfusion when a patient's haemoglobin fell below $10\,g\,dL^{-1}$, a trigger that was proposed in a 1942 paper[3].

The Canadian team, led by epidemiologist and critical-care specialist Paul Hébert, put this widely used threshold to the test. The researchers randomly assigned 838 intensive-care patients to two groups: those in one group would receive a transfusion if their haemoglobin levels fell below $10\,g\,dL^{-1}$, and the other if their levels dropped under $7\,g\,dL^{-1}$.

After 30 days, all the people in the first group had received a transfusion, each receiving an average of 5.6 units of red blood cells (a unit is the amount extracted from around 500 mL of donated blood). Patients in the more restrictive group got just 2.6 units, on average, and one-third of the group received no blood at all.

> "WEANING DOCTORS OFF THEIR LOVE AFFAIR WITH BLOOD IS GOING TO BE HARDER THAN WE THINK."

Yet the probability of death remained the same in both groups. And when the researchers analysed two subgroups of patients — those under 55 years old and those with milder illnesses — they found that the restrictive approach had actually reduced mortality.

"When we saw the results, the first thing I asked the statistician was, 'Are you sure the group assignment was correct?'" recalls Hébert, who is now at the University of Montreal in Canada. "And then we proceeded to check all of our results because, frankly, we didn't believe it."

The team published its results in the *New England Journal of Medicine*[4] in 1999. It was just one trial, but it got people's attention, says Lawrence Tim Goodnough, director of the transfusion medicine programme and transfusion services at Stanford University Medical Center. "Everybody saw that and said, 'We need to redo this in other clinical settings'."

Between 2007 and 2014, at least six more large, randomized trials were published[5–10], each comparing restrictive guidelines to liberal ones. These trials enrolled patients with a wide variety of conditions — septic shock, traumatic brain injuries, gastrointestinal bleeding — as well as children in intensive care, adults undergoing cardiac surgery and older adults having hip surgery. All six studies revealed that patients fare just as well, and sometimes better, when doctors use lower haemoglobin thresholds.

RISKY MEDICINE

Researchers are now trying to understand why transfusions do not always have their intended benefits. It could be that haemoglobin levels are not a good proxy for what doctors really care about, which is whether enough oxygen is actually being delivered to tissues. Or it could be that the blood people are receiving is not doing its job properly.

Fresh red cells are flexible, and flow easily through the body's tiniest capillaries. But after a few weeks in a blood bank, their membranes stiffen. The cells change shape, become stickier and cling more tightly to oxygen. These changes, known as the storage lesion, could make red blood cells less effective. "This may explain why the so-called 'gift of life' isn't translating into benefit for patients," Goodnough says. Research has yielded contradictory findings as to whether the storage lesion actually worsens patient outcomes, but the results of a large randomized trial are expected later this year.

Transfusions not only have uncertain benefits, they also have risks. They can transmit infectious diseases, overwhelm the heart and injure the lungs. They can also wreak havoc on the immune system. "Blood is analogous to a liquid organ transplant," Frank says. "It's foreign tissue from another person." Doctors can prevent most catastrophic immune responses by ensuring that donor and recipient are compatible for the proteins or carbohydrates known as antigens that characterize the ABO and Rh blood types. But blood cells contain many other antigens, and incompatibilities can spark immune reactions that range from mild to fatal.

Paradoxically, transfusions can dampen the immune response and leave patients more vulnerable to infection, although the mechanism behind this remains uncertain.

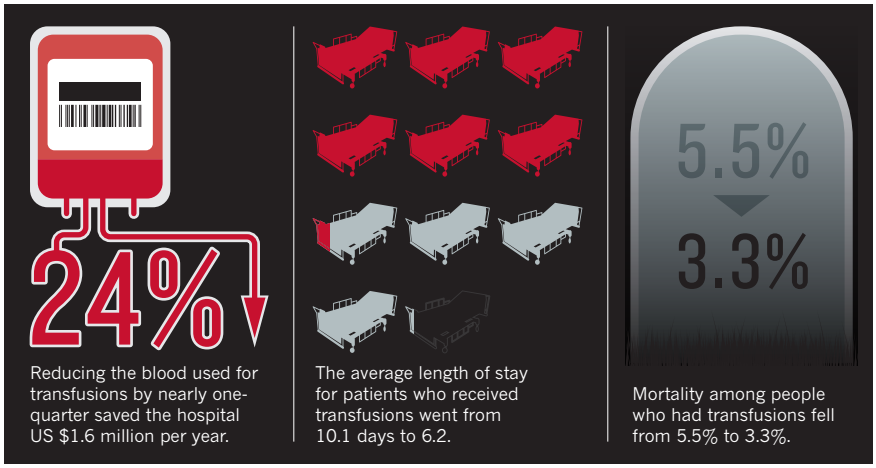
These risks may have gone unnoticed because they are not easy to observe in the course of day-to-day practice. Many people who receive transfusions are already critically ill, and infections are not uncommon in hospitals. The elevated risk that accompanies transfusions becomes apparent only when scientists analyse large patient populations.

For some patients, of course — especially those who are rapidly losing a lot of blood — transfusions are lifesaving. In a study published last year[11], Roberts and his colleagues found that transfusions were beneficial only to those with the most severe injuries — they actually increased mortality in people with mild injuries. And where the line should be drawn is not completely settled: there have not yet been any large, randomized trials examining whether lower thresholds are appropriate for patients having heart attacks or strokes, for example. In January, scientists unexpectedly found that liberal transfusion strategies yield better outcomes in people having surgery for cancer[12]. The complexities of individual ailments and risk factors means that doctors still need to exercise their clinical judgement when deciding whether to prescribe a transfusion.

Nevertheless, experts say, it is evident that many patients have been getting unnecessary transfusions. As Roberts puts it: "There

DOCTOR'S ORDERS

By simply reminding doctors of the current guidelines when they order blood, a California hospital was able to save money and lives.



Reducing the blood used for transfusions by nearly one-quarter saved the hospital US $1.6 million per year.

The average length of stay for patients who received transfusions went from 10.1 days to 6.2.

Mortality among people who had transfusions fell from 5.5% to 3.3%.

SOURCE: REF. 2

are some patients who will die without transfusions and there are some that will die because of transfusion."

A CLINICAL EVOLUTION

The conservative approach is starting to gain acceptance among clinicians. More and more medical associations and professional organizations now recommend haemoglobin thresholds of around 7 g dL^{-1} to 8 g dL^{-1} — and hospitals are implementing strategies to reduce the odds that a patient will need a transfusion in the first place. Doctors are administering iron supplements to people with anaemia who are scheduled for elective surgery, minimizing the amount of blood drawn for laboratory tests and using 'cell salvage' techniques that collect and then re-infuse the blood a patient loses during surgery. Many of these measures have long been used to treat Jehovah's Witnesses, who object to transfusions on religious grounds; now they are being applied to the broader population.

"We're seeing more and more countries coming on board, asking for help in setting up patient blood-management programmes," says Aryeh Shander, executive medical director of the Institute for Patient Blood Management and Bloodless Medicine and Surgery at Englewood Hospital and Medical Center in New Jersey.

The Netherlands has been at the cutting edge. In 2000, it adopted a transfusion threshold of 6.4 g dL^{-1} for otherwise healthy patients, and at least one blood bank reported a 12% decline in transfusions by 2009. And changes to blood-management programmes, new clinical guidelines and a shift towards less-invasive surgical techniques have led to declines in many other countries. In the United Kingdom, for example, the demand for red blood cells dropped by one-fifth between 1999 and 2012. And in the United States, the number of transfused units of whole blood and red blood cells fell by 8% between 2008 and 2011, the latest year for which data are available. The AABB, formerly known as the American Association of Blood Banks, predicts that statistics to be released later this year will show a further 10% drop. Since 2001, the proportion of US hospitals that have had to cancel elective surgery because of a blood shortage has also steadily fallen.

Few believe that it is time for donors to stop rolling up their sleeves. There may still be shortages in some regions or in the aftermath of major disasters, and doctors anticipate an ongoing need for certain blood types and components, such as platelets, which do not last long in storage.

But there is still plenty of room to reduce demand, says AABB chief executive Miriam Markowitz. A 2011 audit[13] of more than 9,000 UK transfusions, for example, found that more than half were potentially avoidable.

Merely changing clinical recommendations may not be enough. "Most people don't pay attention to guidelines," says Victor Ferraris, a cardiothoracic surgeon at the University of Kentucky in Lexington. And that may be particularly true when the guidelines seem to contradict first-hand observations. "Surgeons are very, very experience-oriented," Ferraris says. "Every surgeon who's ever lived has seen someone's life saved by a blood transfusion."

A study[14] published last October illustrates the challenge. When scientists surveyed doctors working at two intensive-care units at Johns Hopkins Hospital, the vast majority of the clinicians reported that the ideal transfusion threshold was 7 g dL^{-1}. But the hospital's electronic medical records revealed that 84% of patients in one unit and 92% in the other received transfusions before their haemoglobin levels fell that low. Some of the doctors deemed their patients too ill for the lower triggers and that the evidence did not apply to them, says David Murphy, the study's first author and a critical-care specialist at Emory University in Atlanta, Georgia. He and his colleagues also found that although doctors generally knew the recommended thresholds, many nurses did not. Nor did the units have a standardized approach, and caregivers rarely discussed the transfusion strategy for individual patients. "If you have ambiguity regarding what we should do for a patient, this greatly influences the likelihood of being able to deliver the right care," Murphy says.

It is possible to overcome these problems, as the Stanford study showed (see 'Doctor's orders'). In the year before the computerized alerts began, just over half of transfusions were done on patients with haemoglobin levels of greater than 8 g dL^{-1}. By 2013, that proportion had fallen below 30%. "The fall-off was very immediate and it's been sustained," says Goodnough, who was the first author on the two papers[1,2] that reported the results.

He thinks that the simple intervention succeeded for multiple reasons. For one thing, doctors may change their behaviour when they think that they are being watched. But the alerts also reminded clinicians about the guidelines, and provided links to the relevant literature. They also forced doctors to slow down and think, rather than defaulting to reflexive and long-ingrained standard procedure.

Finally, they may have provided an opening for caregivers to discuss the needs of individual patients. "Maybe the intern, who was ordering the blood because they were told to, goes back to the team and says, 'I have to give a reason', and then they discuss it," Goodnough says. The clinicians might decide to order the blood anyway, of course. Or they might stop, consider the evidence, and come to agree with what Goodnough believes is its clear message. "The safest blood transfusion," he says, "is the one not given." ■

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